following administration said formulation exhibits a lag in release, producing a bisoprolol plasma concentration of not more than about 1 ng/ml for at least about three hours, and thereafter provides a sustained release of bisoprolol that produces a therapeutic plasma concentration not later than about 12 hours following administration, and wherein said formulation maintains a therapeutic plasma concentration of bisoprolol for the remainder of a twenty-four hour period measured from administration.

REMARKS

In the Office Action dated January 28, 2003, the Office considered claims 1, 3-8, 10-25, and 28-42 and rejected those claims. In this Amendment, claim 1 is amended and claims 37-39 are canceled. Thus, claims 1, 3-8, 10-25, and 28-38 and 40-42 are pending following entry of this Amendment.

Claim Rejections – 35 U.S.C. § 112

The Office rejects claims 37-39 under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation of "substantially purified." In response, Applicants submit that the term is sufficiently definite and that one skilled in the art would understand the metes and bounds of the claims. The specification uses the term at page 4, lines 20-24, and makes clear its meaning in that passage. Nevertheless, solely in an effort to advance prosecution, Applicants have canceled claims 37-39.

Claim Rejection – 35 U.S.C. § 102

The Office rejects claims 1, 3-6, 10-25, and 28-42 under 35 U.S.C. § 102(b) as being anticipated by Noda et al. (U.S. Patent No. 5,137,733). In response, Applicants respectfully submit that Noda et al. does not anticipate the presently claimed invention.

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Applicants' claimed formulation comprises at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer that exhibits a pH-dependent dissolution profile and that imparts a pH-dependent and pH-independent delay in bisoprolol release. Noda et al. does not disclose such a formulation.

Noda et al. makes clear that its formulations are designed for dissolution that is independent of the pH. See, for example, the Abstract ("dissolution pattern irrespective of the PH of a dissolution medium"), Background of the Invention ("An object of this invention . . . and the rate of the dissolution of the medicinal compound does not depend on the pH of a medium for the dissolution"), and Test Example 1 (column 7, lines 7-9: "This result shows that the pharmaceutical preparation of the present invention has the pH-independent dissolution property.") Thus, the very heart of Noda et al.'s invention is to prepare a formulation that releases drug in a manner that is independent of the pH of the media.

Additionally, the exemplified polymers described in Noda et al., Eudragit RS and RL, are well known in the art as exhibiting a pH-independent dissolution profile. The manufacturer, Röhm Pharma, describes Eudragit RS and RL as "pH independent polymers." (Röhm Pharma web page attached.) Indeed, Applicants' own specification states the Eudragit RS and RL "are insoluble in pure water, dilute acids, buffer solutions or digestive fluids *over the entire physiological pH range*." (Sentence spanning pages 11-12, emphasis added.) Thus, Noda et al. very clearly describes and exemplifies formulations that are formulated to dissolve and release drug independently of pH.

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Applicants' claimed invention, on the other hand, is formulated to exhibit a release of bisoprolol that is affected by the pH of the media. As noted above, Applicants' claimed formulation comprises "at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer *that exhibits a pH-dependent dissolution profile and that imparts a pH-dependent and pH-independent delay in bisoprolol release*." Unlike Noda et al.'s polymer system, Applicants' claimed polymer system exhibits a pH-dependent dissolution profile. By this pH-dependent dissolution profile, Applicants' polymer system is able to impart a pH-dependent delay in bisoprolol (drug) release. This is also very clearly different from the Noda et al. formulation.

Applicants respectfully submit that the Noda et al. disclosure cannot anticipate the presently claimed invention, as it is directed to a completely different type of formulation. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Claim Rejections – 35 U.S.C. § 103

The Office rejects claims 1, 3-6, 10-25, and 28-42, under 35 U.S.C. § 103(a) as being unpatentable over Noda et al. In response, Applicants submit that Noda et al. does not render obvious the presently claimed invention.

As noted above, Applicants' claimed formulation comprises at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer that exhibits a pH-dependent dissolution profile and that imparts a pH-dependent and pH-independent delay in bisoprolol release. Noda et al. does not render obvious such a formulation.

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Without presenting the details again, Applicants summarize that Noda et al. is directed to a pH-independent formulation, and that independence of pH is emphasized. The polymers that Noda et al. exemplifies are recognized in the art as pH-independent. And the experiments described in Noda et al. show a formulation that exhibits a pH-independent drug release profile. Clearly, pH-independence is at the very heart of the Noda et al. teaching.

The present invention, on the other hand, relies on the use of a polymer system for which the dissolution *depends* on the pH of the media. Applicants' claimed invention is specifically formulated to exhibit a release of bisoprolol that is affected by the pH of the media. As noted above, Applicants' claimed formulation comprises "at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer *that exhibits a pH-dependent dissolution profile and that imparts a pH-dependent and pH-independent delay in bisoprolol release*." By its pH-dependent dissolution profile, Applicants' polymer system is able to impart a pH-dependent delay in bisoprolol release. This is very clearly different from the Noda et al. formulation.

Indeed, Noda et al.'s teaching goes in a direction opposite of Applicants' claimed invention. Whereas Noda et al. emphasizes a pH-independent formulation, Applicants' claimed invention includes a pH-dependent polymer system. Noda et al., in fact, teaches away from Applicants' claimed invention.

Moreover, as Noda et al. actually teaches away from the presently claimed invention, it cannot possibly suggest Applicants' invention. There is simply nothing in Noda et al. that would suggest or lead to the selection of a polymer exhibiting a pH-

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dependent rate of dissolution. There is nothing whatsoever in Noda et al. that would lead to Applicants' presently claimed invention.

The Office rejects claims 7 and 8 under 35 U.S.C. § 103(a) as being unpatentable over Noda et al. in combination with Oshlack et al. (U.S. Patent No. 5,580,578). In response, Applicants submit that the combination of Noda et al. with Oshlack et al. does not render the claimed invention obvious.

The deficiencies of Noda et al. are discussed above. To recap, Noda et al. does not teach or suggest Applicants' claimed invention, i.e., a formulation comprising "at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer *that exhibits a pH-dependent dissolution profile and that imparts a pH-dependent and pH-independent delay in bisoprolol release*." Indeed, Noda et al. actually suggests that drug release should be pH-*independent*.

Oshlack et al. is similar in its preference for pH-independence. For example, in describing a controlled release dosage form, Oshlack et al. states that its "polymer preferably has a permeability which is unaffected by the pH conditions prevailing in the gastrointestinal tract." (Column 4, lines 20-23.) "In certain preferred embodiments of the present invention, the hydrophobic acrylic polymer is comprised of copolymerizates of acrylic and methacrylic acid esters having a permeability which is unaffected by the pH conditions prevailing in the gastrointestinal tract." (Column 5, lines 16-20.) "In certain preferred embodiments, the hydrophobic acrylic polymer coatings of the present invention have a solubility and permeability independent of the pH of the fluid present in the environment of use." (Column 7, lines 39-42.) Other examples of references to pH-

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independence are made at column 8, lines 11-21 and column 9, lines 63-65. While reference to pH-dependent polymer systems is made (see column 10, lines 6-10), those references are in the minority and are not described as "preferred." Thus, Oshlack et al. leads the reader in the same direction as Noda et al. – away from the present invention.

Thus, the combination of Noda et al. with Oshlack et al. does not teach or suggest the presently claimed invention. Both disclosures emphasize a preference for pH-independence, whereas the claimed formulation relies on a pH-dependent polymer system. Both disclosures teach away from the presently claimed invention.

In view of the foregoing, Applicants respectfully request withdrawal of the rejections for obviousness over Noda et al. alone or in combination with Oshlack et al.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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APPENDIX TO AMENDMENT

Claim 1 is amended as follows:

1. (TWICE AMENDED) A multiparticulate bisoprolol formulation for once-daily oral administration, said formulation comprising at least two particles comprising a core of bisoprolol or a pharmaceutically acceptable salt thereof, and a polymeric coating comprising at least one polymer that exhibits a pH-dependent dissolution profile and imparts a pH-dependent and pH-independent delay in bisoprolol release, wherein following administration said formulation exhibits a lag in release, producing a bisoprolol plasma concentration of not more than about 1 ng/ml for at least about three hours, and thereafter provides a sustained release of bisoprolol that produces a therapeutic plasma concentration not later than about 12 hours following administration, and wherein said formulation maintains a therapeutic plasma concentration of bisoprolol for the remainder of a twenty-four hour period measured from administration.

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